Mesenteric Near-Infrared Spectroscopy and risk of gastrointestinal complications in infants undergoing surgery for congenital heart disease

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ABSTRACT

Near infra-red spectroscopy (NIRS) has been shown to estimate regional perfusion in a number of anatomical sites. We hypothesized that NIRS estimation of mesenteric regional perfusion (rSO2) could identify children at risk of gastrointestinal morbidity. We studied a population of neonates and infants, weighing less than 10kg following cardiac surgery with RACHS-1 score 2 or above. We evaluated mesenteric NIRS, central venous oxygen saturation and arterial blood gases for 48 hours post-operatively. Enteral feeding intake, GI complications and markers of organ dysfunction were monitored for 7 days. Fifty children, with median age of 16.7 (3.2 – 31.6) weeks were studied. On admission the average mesenteric NIRS was 71 ± 18 % and the systemic oxygen saturation was 93 ± 7.5%. Admission mesenteric NIRS showed an inverse correlation with time to establish enteral feeds ($r= -0.58$, $p<0.01$) and a direct correlation with duration of feeds at 7days ($r=0.48$, $p<0.01$). Children with GI complications had significantly lower admission mesenteric NIRS (58 ± 18 % vs. 73 ± 17 %, $p=0.017$] and higher mAVDO2 at admission [39 (23-47) % vs 19 (4 – 27) %, $p=0.02$]. On multiple logistic regression, admission mesenteric NIRS was independently associated with GI complications (OR, 0.89; 95% CI, 0.8 – 0.99; $p=0.04$). Admission mesenteric NIRS showed an area under the ROC curve of 0.76 to identify children who developed GI complications, with a suggested cut-off value of 72% (78% sensitivity, 68% specificity).We conclude that admission mesenteric NIRS is associated with GI complications and enteral feeding tolerance in children post cardiac surgery.

Keywords: Near-Infrared Spectroscopy; feeding tolerance; Congenital Heart Disease; Mesenteric Perfusion; gastrointestinal complication; cardiac surgery.

Introduction

Gastrointestinal morbidity in neonates and infants after cardiac surgery is common and can have devastating consequences.[1-3]The reported incidence of necrotizing enterocolitis (NEC) is between 3.3% and 13% in cardiac neonates. Feeding intolerance is also common, particularly in children with single ventricle physiology.[2] Although the pathophysiology of NEC remains unclear, evidence suggest that, in the cardiac population, intestinal ischemia plays a critical role.[4] Compromised perfusion can also, conceivably, be linked with poor gut motility and feeding intolerance. [5]Reduced mesenteric flow and tissue hypoxia may occur before, during and after surgery for congenital heart defects.[6,7,8] Intraoperative factors such as cardiopulmonary bypass (CPB) and hypothermia and postoperative low cardiac output and imbalances between systemic and pulmonary circulations can compromise gut perfusion and predispose to intestinal mucosal injury.[9, 10]

Near Infra-Red Spectroscopy (NIRS) provides a non-invasive, real time and sensitive estimation of regional venous oxygen saturation (rSO2), and can potentially detect early changes in organ perfusion. [11-16] Use of NIRS to estimate mesenteric rSO2 has been shown to correlate with markers of intestinal perfusion (i.e., gastric tonometry) in infants after surgery for congenital heart disease.[17] Cerebral and renal rSO2 following cardiac surgery have been found to be associated with increased post-operative morbidity.[18,19,20] We, therefore, hypothesized that NIRS estimation of mesenteric rSO2 could identify children at risk of gastrointestinal complications following surgery for congenital heart disease.

Materials and methods

Patients: The study was prospectively approved by the Institutional Research and Development Department at the Royal Brompton Hospital (London, UK). Given the non-interventional nature of the study, parental consent was waived. All children less than 1 year of age, weighing less than 10Kg, who underwent a corrective or palliative surgical procedure with cardiopulmonary bypass for a congenital cardiac lesion ranked RACHS-1 score 2 or above were deemed eligible.[21] Patients with a known

gastrointestinal anomaly (including previously diagnosed gastroesophangeal reflux disease) were excluded from the study. Patients were recruited consecutively, and data collection was undertaken prospectively by the study investigators. Clinical management was at the discretion of the attending clinician. The diagnosis of any morbidity and management of organ dysfunction including inotrope usage and the progression of feeds was undertaken by the attending clinicians, and was independent of the data collection. All values for rSO2 were collected continuously using a NIRS monitor (see below). Due to the nature of the study, the clinical team was not blinded to the data from the NIRS monitor.

NIRS Monitoring: An INVOS 5100 device (Somanetics, Troy, MI) was used to monitor rSO2. NIRS relies on the Beer-Lambert law and the fact that hemoglobin has different absorbance spectra depending on its oxygenation status. The INVOS device emits near infrared light at two wavelengths (730 and 805 nm) which corresponds to the spectral absorption of oxygenated and deoxygenated hemoglobin and employs 2 detectors to measure the intensity of the reflected light. The difference in intensity of the detected light can be used to calculate the oxyhemoglobin-to-deoxyhemoglobin ratio and ultimately be expressed (using a proprietary calculation) as a regional oxygen saturation. Subtracting from two different source detector positions (one detector is closer to the source and measures superficial tissue oxygenation) eliminates the effect of superficial tissues.

Each eligible patient enrolled in the study had NIRS monitoring started on arrival to PICU after surgery (within 30 minutes). Self-adhesive Somasensors (neonatal for patients less than 4 kg and pediatric otherwise, Somanetics Corp) were placed 2 cm below the umbilicus (mesenteric) and attached to a Somanetics NIRS monitor. Postoperative NIRS monitoring continued for maximum 48h or until the patient was moved from the intensive care unit to high dependency care (i.e. that they were extubated and off inotropic support) for patients transferred before 48h. Data collection of outcome variables continued for 7 days.

The usual feeding practice for postoperative patients in our Unit is to initiate nasogastric feeds as soon as possible at the discretion of the Attending Intensivist once hemodynamic stability has been achieved and end organ perfusion is satisfactory. Typically, the use of epinephrine at doses higher than 0.03 micrograms per kilogram per minute (mcg/kg/m) as well as the use of norepinephrine and vasopressin is considered contraindications to enteral feeding. Low dose epinephrine is a relative contraindication. We start feeds with 20 kcal per ounce (30ml) of formula (breast milk or other standard formula based on cow's milk). Human breast milk (maternal or donor) is preferred over formula milk. For high risk patients, we start at 0.5 milliliters per kilogram per day (ml/kg/d) and advance by 0.5ml/kg/day every 12 hours. For intermediate risk patients, we typically start at 1ml/kg/h and advance by 1ml/kg every 8 hours and for low risk patients, we start at 1ml/kg/h and advance by 1ml every 4 hr. We typically start with hourly bolus feeds until we achieve full volume of feeds (120 ml/kg/day) and we then condense to 2 hourly and 3 hourly feeds. Once feeds are tolerated at volumes of 120 ml/kg/day as 3 hourly bolus feeds, we start increasing caloric density by increments of 2 kcal per ounce daily up to 30 kcal per ounce if required. Nutritionists are part of the multidisciplinary team that round daily on each patient and play significant role in determining feeding plan. Typically, parenteral nutrition is discontinued when 2 ml/kg/h of enteral feeds are tolerated. Abdominal distention, 2 or more episodes of emesis over 12h and increased gastric residuals (more than 50% of 4 hourly feeding volumes) are considered triggers for a diagnostic evaluation for feeding intolerance. The diagnosis of feeding intolerance is left at the discretion of the clinical team and typically requires 2 or more of the above symptoms/signs that led to cessation of feeds for more than 4 hours and re-initiation at a lower rate. We view feeding intolerance in the postoperative cardiac patient as potential early sign of compromised gut perfusion and we take aggressive action to avoid progression to necrotizing enterocolitis. We typically include abdominal radiographs and inflammatory markers in our diagnostic work up. We consider post pyloric feeds only if impaired gut perfusion and necrotizing enterocolitis has been ruled out.

Data collection: Data collection was performed by two of the investigators (I.I, R.G.B) not directly involved in the clinical care of the patients. Continuous NIRS data was recorded using a USB drive for the study period for each subject. Demographic data, co-morbidities and procedural variables were collected from the medical records. Physiologic variables (heart rate, Mean Arterial Pressure MAP, temperature, pulse oximetry) and laboratory data were extracted from the patient's electronic medical record (CareVue) where physiologic and clinical variables were recorded hourly by the bedside nurse and blood gas and laboratory results appear automatically. Blood gases and laboratory results were obtained at the discretion of the clinical team as per standard clinical care in our unit. Central venous saturations were obtained from blood gases taken from indwelling catheters in the superior cava vein (SVC).

Definitions: **Mesenteric NIRS** was defined as the rSO2 estimation using NIRS (as described above). This was a continuous measurement during the first 48hours of admission or until the time of transfer out of the intensive care unit; **admission mesenteric NIRS** was defined as the rSO2 reading on the NIRS monitor when the first blood gas was obtained (within 15 minutes of starting NIRS monitoring); **mean mesenteric NIRS** was the average of the mesenteric NIRS readings for each patient; **mesenteric arteriovenous difference of oxygen (mAVDO2)** was estimated subtracting NIRS saturation from arterial oxygen saturation (from arterial blood gas). **Time to establish enteral feeding** was defined as the length of time from PICU admission to the time the child tolerated more than 2ml/kg/h of enteral feeds; **Feed intolerance** was defined by our unit protocol as described above; **Duration of feeds** was defined as the time (in hours) that enteral feeding was tolerated from PICU admission until day 7; **Necrotizing enterocolitis (NEC)** was a clinical diagnosis by the attending team based on clinical, biochemical and radiographic evidence as defined in the modified Bell staging criteria.[22] **GI complication** was defined as the presence of NEC, feed intolerance, GI bleed, or any GI abnormality associated with cardiac surgery.[23] Diagnosis of morbidity was made independently by the attending clinical team. All data was collected from patient notes by the investigating team using the defined criteria described above.

Data analysis:

Statistical analyses were performed using the Statistical Package for the Social Sciences 17.0 for Windows (SPSS, Chicago, IL) and the Statistical Discovery software (JMP Statistics, SAS Institute, Cary, NC). Categorical data were expressed as proportions, and groups were compared using the chi-square test. Continuous variables were expressed as median with interquartile range. Comparisons between groups were performed using student T test for variables with normal distribution, and Mann-Whitney U test for variables with non-normal distribution. Correlations were performed using Pearson test for variables with normal distribution, Spearman test for variables with non-normal distribution. Variance inflation factor was used to identify multicollinear variables. Dummy coding was performed for analysis of categorical variables. The possible factors associated with GI complications were evaluated using univariate analysis. Those factors that showed $p < 0.15$ by univariate analysis were evaluated using multivariate logistic regression. The area under the receiver operating characteristic (ROC) curve was used to assess the ability of mesenteric NIRS to predict GI complications. Also, multiple regressions were performed to identify clinical variables predicting mesenteric NIRS and variables associated with PICU length of stay. Statistical significance was defined at $p < 0.05$.

Results

Patient Characteristics

Fifty children were included in the study, of which 34 (68%) were boys. No child was excluded. The median age was 16.7 (3.2 – 31.6) weeks and fifteen (30%) subjects were neonates. The median weight was 4.8 (3.8-6.82) kg. Further clinical characteristics are shown in Table 1.The mean RACHS-1 score was 2.66 ± 0.86 and the most common diagnoses were Transposition of the Great Arteries (20%) and Tetralogy of Fallot (18%). Eight (16%) children had single ventricle anatomy. The median duration of mechanical ventilation was 2.3 (1.1 – 5.6) days and the median length of PICU stay was 5 (2.9 – 7.9) days. The median time to establish enteral feeds was 48 (26 – 102) hours. Nine (18%) children had GI

complications, of which 3 (6%) had confirmed and 1 (2%) had suspected necrotizing enterocolitis, the remaining had abdominal distention and feed intolerance. Two (4%) children died.

On admission following surgery, the average value for mesenteric NIRS was 71 ± 18 % and the systemic oxygen saturation was 93 ± 7.5%, with a median mAVDO2 of 21 (6.7-33)%. The duration of mesenteric NIRS monitoring was 45 ± 7 hours. Average of all mesenteric NIRS values during the study period was 69 ± 14 %. Although systemic saturation was significantly lower in children with univentricular physiology in comparison to children with biventricular physiology following surgery (81 ± 8 % vs. 95 ± 5 %, $p<0.01$), mesenteric NIRS was similar between these groups on admission (68 ± 25 % vs. 70 ± 16%, $p=0.5$) and during the whole study (66 ± 21 % vs. 69 ± 13 %, $p=0.5$).

Mesenteric NIRS as predictor of feeding outcomes and gastrointestinal morbidity following surgery for congenital heart disease

Admission mesenteric NIRS showed an inverse correlation with time to establish enteral feeds ($r= -0.58$, $p<0.01$) and a direct correlation with duration of feeds at 7 days ($r=0.48$, $p<0.01$). Admission mAVDO2 showed a direct correlation with time to establish enteral feeds ($r = 0.52$, $p<0.01$) and an inverse correlation with duration of feeds at 7 days ($r = -0.51$, $p<0.01$). Children with GI complications had significantly lower admission mesenteric NIRS (58 ± 18 % vs. 73 ± 17 %, $p=0.017$] and higher mAVDO2 at admission [39 (23-47) % vs 19 (4 – 27) %, $p=0.02$].

Univariate analysis identified admission mesenteric NIRS, admission mAVDO2, RACHS>3, weight, lactate, and ScvO2 as possible factors associated with GI complications (all $p<0.15$) (Table 2). Interestingly, univentricular physiology was not associated with GI complications. Nor was there any significant difference in admission or mean NIRS between those with univentricular and biventricular physiology. On multiple logistic regression only admission mesenteric NIRS was independently associated with GI complications (OR, 0.89; 95% CI, 0.8 – 0.99; $p=0.04$) [both admission and mAVDO2

were independently associated with GI complications, but these variables were multicollinear and we kept the variable with the strongest association with GI complications, i.e., admission mesenteric NIRS].

One important aspect of rSO2 monitoring would be to develop a predictive model to help evaluate risk of complications. Since admission mesenteric NIRS was strongly associated with GI complications in our study, we went on to evaluate the ability of admission mesenteric NIRS to discriminate between children who subsequently went on to develop GI complications.

The ability of admission mesenteric NIRS to discriminate children with GI complications was assessed using the ROC curve. Admission mesenteric NIRS showed an area under the ROC curve of 0.76 to identify children who developed GI complications (Figure 1), suggesting that admission mesenteric NIRS is a good discriminator of GI outcome. A cut-off value of 72% showed a sensitivity of 78% with a specificity of 68% while a cut-off value of 75% showed a sensitivity of 89% with a specificity of 51%.

We also studied factors associated with the time to establish enteral feed. On univariate analysis, the variables potentially associated with the time to establish enteral feed were admission mesenteric NIRS, admission mAVDO2, lactate, age, and weight (all $p<0.15$). On multiple regression analysis only lactate and admission mesenteric NIRS (or mAVDO2, multicollinear variables) were independently associated with time to establish feeds ($p <0.01$ for both).

Contribution of impaired mesenteric perfusion to other markers of clinical morbidity

We explored the association between admission mesenteric NIRS and clinical outcomes or markers of disease severity. Admission mesenteric NIRS showed weak, but statistically significant linear correlations with the worst lactate and ScvO2 levels during admission (r 0.33 and 0.27, respectively, $p<0.05$ for both) and with the time free of PICU at 28 days (r 0.28, $p<0.05$). Children with admission mesenteric NIRS lower than 75% had higher admission lactate, and longer duration of mechanical ventilation and PICU stay than children with mesenteric NIRS $\geq$ 75% (p values 0.05, 0.01, 0.04, respectively). There was no

association between NIRS and inotrope requirement (inotrope score), core temperature, or post-operative renal function (plasma creatinine), or maximum hepatic enzymes (levels of AST and ALT) (all $p>0.05$)

Discussion

In this study we found that mesenteric NIRS is associated with enteral feeding outcomes, such as duration of feeds and time to achieve full enteral feedings. We also found that mesenteric NIRS on admission to PICU is an independent risk factor for development of GI complications.

GI complications are relatively common and potentially serious adverse events in infants undergoing surgery for congenital heart disease. [1-3, 8]The current management of gastrointestinal health and feeding strategies following congenital heart surgery is largely based on clinical observation, and no specific markers of safety or viability are routinely used in clinical practice. Evaluation of gut mucosal perfusion could provide a direct method to identify patients at risk of developing GI complications and allow clinicians to stratify feeding and gut protective strategies objectively. Monitoring of mesenteric NIRS is a simple and non-invasive technique that provides real-time and continuous information on GI perfusion. This makes mesenteric NIRS an ideal candidate to guide therapy and stratify young children for interventions to protect the gut following surgery for congenital heart disease. There is growing evidence to support the use of NIRS as a marker of regional perfusion in critical vascular beds and its correlation with adverse clinical outcomes. Intraoperative low cerebral NIRS has been associated with increased risk of cognitive delay in adults undergoing coronary artery bypass grafting.[18]In the pediatric cardiac population, both cerebral and renal NIRS have been associated with clinical outcomes. In particular, perioperative low cerebral NIRS is associated with poorer neurodevelopment at 1 year post surgery[19] and flank (renal) NIRS with postoperative renal dysfunction in cardiac neonates.[20]

To our knowledge, our study is the first report to correlate post-operative mesenteric oxygenation measured by NIRS with adverse gastrointestinal outcomes in children following congenital heart disease surgery. The link between mesenteric NIRS and enteral feeding has, however, already been described in

the (non-cardiac) neonatal population. Mesenteric NIRS has been shown to increase in response to enteral feeding [24] and to be reduced in neonates with abdominal pathology.[25] Animal studies have confirmed the association between mesenteric NIRS, mesenteric perfusion, and GI complications. Low mesenteric NIRS were described in animal models of abdominal compartmental syndrome, [26] hemorrhagic shock, [27] feed intolerance [28] and NEC. [29]

It is interesting that in our data the admission mesenteric NIRS had the strongest association with GI complication. Both the average mesenteric NIRS during the study (45 hours) and the mAVDO2 were statistically associated with GI complications but these associations were weaker than the admission mesenteric NIRS. Critical changes during surgery (such as cardiopulmonary bypass and hypothermia) can have a damaging effect on gut mucosa and increase risk of developing GI complications.[10]Further work should include an assessment of the association between intraoperative mesenteric NIRS and clinical outcomes. We were surprised that the PICU admission mesenteric NIRS was similar in children with univentricular and biventricular physiology. It contrasts to previous studies showing reduced mesenteric flow[7] and higher incidence of NEC [1] in the single ventricle population. Explanation of this finding is problematic. Our study included only 8 children with single ventricle physiology. Given that the standard deviation of mesenteric NIRS was high, the small size of this group may partly explain this unexpected finding. Furthermore, 6 out of our 8 single ventricles were patients after bidirectional Glenn procedure with excellent hemodynamics, cardiac output and end-organ perfusion. However, further studies in larger populations are needed to address this paradoxical observation.

We identified an admission NIRS value of less than 75% as being a good predictor of adverse GI outcome. Further validation could allow a threshold such as this to be used in risk stratification, feeding and treatment plans.

Our study has several limitations that need to be discussed. First, we studied a small cohort of 50 children. Larger cohorts of patients will be needed to establish mesenteric NIRS thresholds that could be

extrapolated to other populations and applied in clinical practice. Second, the mesenteric NIRS reading could be adversely affected by severe edema, ascites or abdominal distention. To minimize this limitation we recruited only children weighing less than 10Kg, where there is good evidence on clinical relevance of rSO2 evaluation.[16,17,19, 30,31] Third, the clinical team was not blinded to the NIRS values. Although this could influence clinical decisions, the outcomes evaluated in our study (enteral feeding and GI complications) were protocol driven and mesenteric NIRS is not currently used as a decision making tool in our service. Last, we did not evaluate intra-operative mesenteric NIRS. This could significantly improve the predictive value of GI complications of children undergoing cardiac surgery.

In conclusion, we found that admission mesenteric NIRS is associated with GI complications and enteral feeding tolerance in children post cardiac surgery. Although further work is needed to validate these findings, our data suggests that admission mesenteric NIRS may be useful in guiding feeding and establishing gut protective strategies in children following cardiopulmonary bypass.

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Conflict of Interest statement:

The authors have no conflict of interest to report

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TABLE LEGENDS:

Table 1: General characteristics of the population

Values shown are median (IQR) or mean (+/- SD) (the latter for normally distributed data).

Table 2: Regression analysis of factors associated with GI complications. Admission mesenteric NIRS was independently associated with GI complications after cardiac surgery.

FIGURE LEGENDS:

Figure 1: Mesenteric NIRS in children with and without GI complication

Bar chart showing mean (+/- SEM) admission mesenteric NIRS in children with and without subsequent GI complications (suspected or proven NEC)

Figure 2: Receiver Operating Characteristic curve for Mesenteric NIRs predicting GI complication

The area under the ROC curve for mesenteric NIRS of 0.76 suggests that mesenteric NIRS is a reasonably good discriminator of adverse GI outcome**.**

Table 1. General characteristics of the population

	All (n=50)
Male	34 (68%)
Age (weeks)	16.7 (3.2 – 31.6)
Neonate	15 (30%)
Weight (Kg)	4.8 (3.6 – 6.8)
RACHS	2.7 ± 0.9
Single Ventricle	8 (16%)
SvO2	59 ± 14
mAVDO2	22 ± 19
Mesenteric rSO2	71 ± 18
Lactate	2.1 ± 1
Time to establish feeds (hrs)	48 (26.5 – 102)
Duration of Inotropes (hrs)	85 (22 – 141)
Ventilation (hrs)	56 (25 – 134)
PICU stay (days)	5 (2.9 – 7.9)
Deaths	2 (4%)

Table 2. Regression analysis of factors associated with GI complications

Univariate Analysis			
	GI Complication (n=9)	**No GI complication (n=41)**	**P**
Gender (male)	5 (56%)	29 (71%)	0.3
Neonate	2 (22%)	13 (32%)	0.4
Weight (Kg)	4.3 ± 1	5.4 ± 2.1	0.06
RACHS	3 ± 0.9	2.6 ± 0.7	0.09
Single ventricle	1 (11%)	7 (17%)	0.3
SvO2*	52.3 ± 20.1	60.5 ± 12.2	0.06
mAVDO2*	35.3 ± 14.7	19.6 ± 19.1	0.01
Mesenteric rSO2*	57.9 ± 17.6	73.5 ± 17.1	<0.01
Lactate	2.5 ± 1.5	2 ± 0.9	0.11

Binary Logistic regression**				
		OR	95% CI	P
Mesenteric rSO2		0.956	0.935 - 0.977	0.03

* SvO2, mAVDO2, and Mesenteric rSO2 are multicollinear variables and were analysed individually in the regression models

** Binary Logistic regression using Forward Stepwise method. The variables weight, RACHS (categorical), SvO2, mAVDO2, and Lactate were tested in the regression but were not included in the final equation/model.

Figure 1

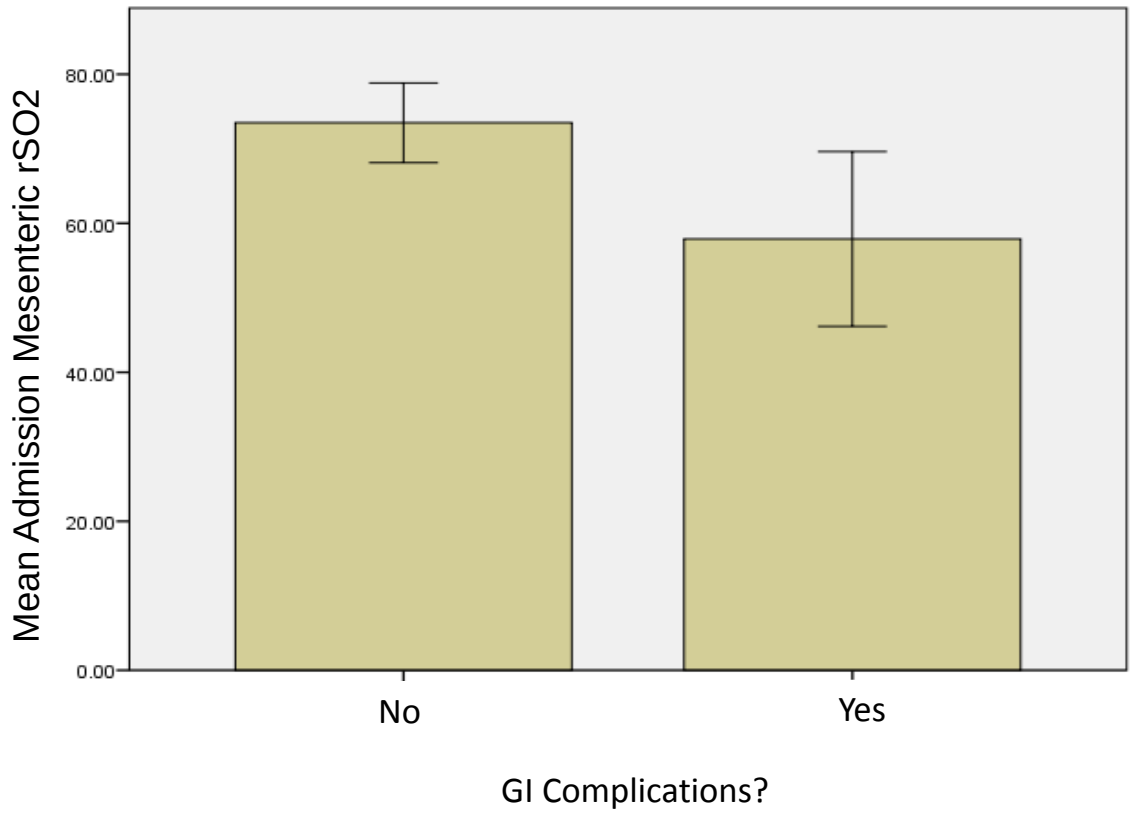
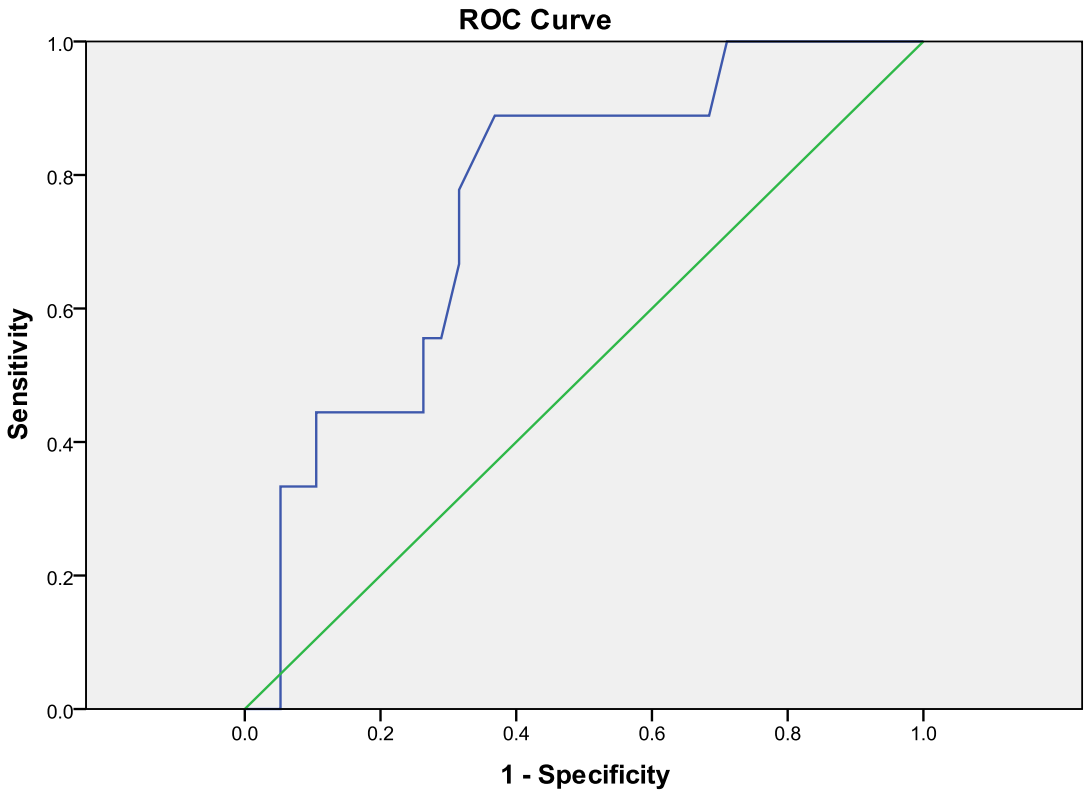

Mean Admission Mesenteric rSO2
80.00
60.00
40.00
20.00
0.00
No
Yes
GI Complications?

Figure 2



Diagonal segments are produced by ties.